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Hypothyroidism correlates with favourable survival prognosis in patients with brain metastatic cancer

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Abstract: BACKGROUND Several preclinical and epidemiologic studies have indicated tumour-promoting effects of thyroid hormones (THs). However, very limited knowledge exists on the prognostic impact of thyroid function in metastatic cancer. METHODS We compiled a discovery cohort of 1692 patients with newly diagnosed brain metastases (BMs) of solid cancers treated at the Medical University of Vienna and an independent validation cohort of 191 patients with newly diagnosed BMs treated at the University Hospital Zurich. RESULTS Hypothyroidism before diagnosis of cancer was evident in 133 of 1692 (7.9%) patients of the discovery, and in 18 of 191 (9.4%) patients of the validation cohort. In the discovery cohort, hypothyroidism was statistically significantly associated with favourable survival prognosis from diagnosis of cancer (31 vs. 21 months; p = 0.0026) and with survival prognosis from diagnosis of BMs (12 vs. 7 months; p = 0.0079). In multivariate analysis including the diagnosis-specific graded prognostic assessment score, primary tumour type and sex, hypothyroidism was an independent factor associated with survival after diagnosis of BMs (hazard ratio: 0.76; 95% confidence interval [CI]: (0.63; 0.91; p = 0.0034). In the validation cohort, the association of hypothyroidism and favourable survival prognosis from diagnosis of cancer (55 vs. 11 months; p = 0.00058), as well as from diagnosis of BMs (40 vs. 10 months; p = 0.0036) was confirmed. CONCLUSION Pre-existing hypothyroidism was strongly and independently associated with prognosis in patients with newly diagnosed BMs, supporting the evidence from preclinical data that THs may indeed have a tumour-promoting effect. Further investigation of the underlying pathobiological mechanism and potential therapeutic implications are required.

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Original Research

Hypothyroidism correlates with favourable survival prognosis in patients with brain metastatic cancer

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Metastatic;
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Abstract ***Background:*** Several preclinical and epidemiologic studies have indicated tumour-promoting effects of thyroid hormones (THs). However, very limited knowledge exists on the prognostic impact of thyroid function in metastatic cancer.
Methods: We compiled a discovery cohort of 1692 patients with newly diagnosed brain metastases (BMs) of solid cancers treated at the Medical University of Vienna and an independent validation cohort of 191 patients with newly diagnosed BMs treated at the University Hospital Zurich.
Results: Hypothyroidism before diagnosis of cancer was evident in 133 of 1692 (7.9%) patients of the discovery, and in 18 of 191 (9.4%) patients of the validation cohort. In the discovery cohort, hypothyroidism was statistically significantly associated with favourable survival

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prognosis from diagnosis of cancer (31 vs. 21 months; p = 0.0026) and with survival prognosis from diagnosis of BMs (12 vs. 7 months; p = 0.0079). In multivariate analysis including the diagnosis-specific graded prognostic assessment score, primary tumour type and sex, hypothyroidism was an independent factor associated with survival after diagnosis of BMs (hazard ratio: 0.76; 95% confidence interval [CI]: (0.63; 0.91; p = 0.0034). In the validation cohort, the association of hypothyroidism and favourable survival prognosis from diagnosis of cancer (55 vs. 11 months; p = 0.00058), as well as from diagnosis of BMs (40 vs. 10 months; p = 0.0036) was confirmed.

Conclusion: Pre-existing hypothyroidism was strongly and independently associated with prognosis in patients with newly diagnosed BMs, supporting the evidence from preclinical data that THs may indeed have a tumour-promoting effect. Further investigation of the underlying pathobiological mechanism and potential therapeutic implications are required.

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1. Introduction

Cancer is a leading cause of death worldwide, even though the development of molecularly targeted therapies has improved patient's survival times [1]. Brain metastases (BMs) occur most frequently in patients with metastatic lung cancer, breast cancer or melanoma and represent a particularly devastating complication, as curative treatments are lacking so far [2]. Furthermore, the neurological symptoms of BMs severely impact the quality of life of affected patients, leaving this cohort in particular clinical need for new therapeutic approaches. Biological factors driving metastatic spread are of high clinical interest for the development of new targeted therapeutic approaches [3].

Thyroid hormones (THs) have been reported to impact cancer growth. Several preclinical studies suggest that TH suppression by pharmacological inhibition or thyroid resection reduces cancer growth rates [4–6]. Epidemiological studies further supported this preclinical observation of TH-induced tumour growth as a higher risk of ovarian, pancreatic, prostate and lung cancer has been observed in patients with hyperthyroidism and subsequent TH excess [7]. In line, patients with hypothyroidism were shown to be older at the diagnosis of breast cancer, suggesting that the metabolic hypothyroid state actually might slow down tumour development and progression [8,9]. However, despite promising evidence from these preclinical and epidemiological investigations, comprehensive analyses of the prognostic impact of thyroid function in patients with frequent cancer types, for example, lung cancer and breast cancer, have not been undertaken. Therefore, we investigated the prognostic impact of thyroid function in a large, well defined cohort of patients suffering from metastatic cancer and BMs, as well as an independent validation cohort to investigate the clinical correlation of thyroid function with survival.

2. Material and methods

2.1. Patients

Patients suffering from metastatic cancer and treated for newly diagnosed BM at the Medical University of Vienna between 1990 and 2017 were identified from the Vienna Brain Metastasis Registry ('discovery cohort'). Further, an independent cohort of patients treated for newly diagnosed BMs at the University Zurich between 2004 and 2017 was identified ('validation cohort'). The discovery and the validation cohort were treated by independent multidisciplinary teams in accordance with good clinical practice guidelines.

History of hypothyroidism was defined as treatment with TH substitution and mentioning of 'hypothyroidism' in the diagnosis section of the patient. Clinical symptoms of hypothyroidism were not reported. Patients with documented hyperthyroidism in their past medical history and/or treatment with thyreostatics were included in the hyperthyroidism group.

A broader spectrum of clinical data was obtained in the discovery cohort including thyroid-stimulating hormone (TSH), as well as free triiodothyronine (fT3), T3, free thyroxine (fT4) and T4 levels. Lower limit of normal, upper limit of normal (ULN) and normal range (NR) were defined in accordance with the central laboratory (Department of Laboratory Medicine, Medical University of Vienna). NR for TSH was .44 to 3.77 μIU/ml, for fT3 2.15–4.12 pg/ml, for fT4 0.76–1.66 ng/dl, for T3 0.8–1.8 ng/ml and for T4 58–124 ng/ml. The diagnosis-specific graded prognostic assessment (DS-GPA) score was calculated based on clinical parameters including age, Karnofsky performance score, number of BMs and status of the extracranial disease [10].

This project was approved by the ethics committee of the Medical University of Vienna (078/2004).

2.2. Statistical analysis

Overall survival from diagnosis of cancer was defined from diagnosis of cancer to death or last follow-up. Time to BM development was defined as time from diagnosis of cancer to diagnosis of BM. Overall survival from diagnosis of BM was defined as the time from radiological BM diagnosis to death or last follow-up. Differences between groups were assessed using the chi square test, the Kruskal-Wallis test, and the Mann-Whitney U test as appropriate. The Kaplan-Meier product limit method was used to estimate survival times, and the log rank test was used to estimate survival differences between groups. For multivariate survival analyses, a Cox proportional hazards model was applied to adjust for other pre-specified prognostic factors such as DS-GPA, classified in class I-IV, primary tumour and sex. Owing to the hypothesis generating design of the present study no correction for multiple testing was applied. A two-tailed p-value ≤ 0.05 was considered to indicate statistical significance. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS®) 23.0 software (SPSS Inc., Chicago, IL, USA) and R version 3.5.1.

3. Results

3.1. Patients characteristics

3.1.1. Discovery cohort

One thousand six hundred ninety-two patients (775 males, 45.8%; 917 females, 54.2%) with a median age at diagnosis of cancer of 59 years (range: 24–89) and a median time of 8 months (range: 0–25) until diagnosis of BMs were included in the discovery cohort. Primary tumours included lung cancer (1183/1692; 69.9%), breast cancer (411/1692; 24.3%) and melanoma (98/1692; 5.8%). None of the included patients were treated with immune checkpoint inhibitor therapy or vascular endothelia growth factor receptor directed tyrosine kinase inhibitors and in consequence none of the observed thyroid dysfunction was caused by systemic treatment. DS-GPA was available for all patients and 180 patients (10.6%) belonged to class I, 578 patients (34.2%) to class II, 632 patients (37.4%) to class III and 302 patients (17.8%) to class IV. Median survival from BM diagnosis in the entire cohort was 7 months (range: 0–196), and only 102 patients (6%) were still alive at the last follow-up. DS-GPA class showed an association with survival from diagnosis of BM in univariate analysis ($p < 0.001$; log rank test). Table 1 lists further characteristics of the discovery cohort.

3.1.2. Validation cohort

One hundred ninety-one patients (113 males, 59.2%; 78 females, 40.8%) with a median age of 63 years (31–89) at the diagnosis of cancer were included in the validation cohort. Primary tumours were lung cancer in 172 patients (90.1%), breast cancer in 4 patients (2.1%), melanoma in 14 patients (7.3%), and a parotid tumour in 1 patient (0.5%). No patient was treated with immune checkpoint inhibitors, and in consequence none of the observed thyroid dysfunctions were caused by such therapy. Table 2 lists further characteristics of the validation cohort.

Table 1
Patient characteristics of the discovery cohort.

Characteristics		n = 1692	%
Age at diagnosis of BM, years	Median	59	
	Range	24–89	
Sex	Male	775	45.8
	Female	917	54.2
Cancer entity	Lung cancer	1183	69.9
	Breast cancer	411	24.3
	Melanoma	98	5.8
Extracranial metastases at BM diagnosis	Yes	695	41.1
	No	997	58.9
DS-GPA score	Class I	180	10.6
	Class II	578	34.2
	Class III	632	37.4
	Class IV	302	17.8
History of thyroid dysregulation prior to cancer diagnosis	None	1526	90.2
	Hypothyroidism	133	7.9
	Hyperthyroidism	33	2.0
Cause of hypothyroidism	Thyroidectomy	26	1.5
	Autoimmune thyroiditis	13	0.8
	Unknown	94	5.6
Hypothyroidism per cancer entity	Lung cancer (n = 1183)	78	6.5
	Breast cancer (n = 411)	49	11.9
	Melanoma (n = 98)	6	6.1

DS-GPA, diagnosis-specific graded prognostic assessment.

3.2. Thyroid function in patients with BMs

3.2.1. Discovery cohort

One hundred thirty-three patients (7.9%) were diagnosed with hypothyroidism and 33 patients (2%) were

Table 2
Patient characteristics of the validation cohort.

Characteristics		n = 191	%
Age at diagnosis of BM, years	Median	62.84	
Sex	Male	113	59.2
	Female	78	40.8
Cancer entity	Lung cancer	172	90.1
	Breast cancer	4	2.1
	Melanoma	14	7.3
	Parotid tumour	1	0.5
History of thyroid dysregulation before cancer diagnosis	None	171	89.5
	Hypothyroidism	18	9.4
	Hyperthyroidism	2	1.0

Table 3
Clinical differences in patients with and without history of hypothyroidism in the discovery cohort.

Characteristics		Patients with history of hypothyroidism (n = 133)		Patients without history of hypothyroidism (n = 1559)		P value
		N	%	N	%	
Age at diagnosis of BM, years	Median	60		58		0.173
	Range	33–88		24–89		
Sex	Male	24	18.0	751	48.2	<0.001
	Female	109	82.0	808	51.8	
Cancer entity	Lung cancer	78	58.6	1105	70.9	0.002
	Breast cancer	49	36.8	363	23.3	
	Melanoma	6	4.5	92	5.9	
Extracranial metastases at BM diagnosis	Yes	85	63.9	912	58.5	0.223
	No	48	36.1	647	41.5	
Karnofsky performance status	Median	80		80		0.694
	Range	30–100		10–100		
Number of BMs	Median	1		2		0.528
	Range	1–20		1–22		
DS-GPA score	Class I	25	18.8	277	17.8	0.761
	Class II	50	37.6	582	37.3	
	Class III	41	30.8	537	34.4	
	Class IV	17	12.8	163	10.5	

DS-GPA diagnosis-specific graded prognostic assessment.

diagnosed with hyperthyroidism before the diagnosis of cancer (Table 1). Twenty-six patients (1.5%) had hypothyroidism due to thyroid surgery for a benign nodule, 13 patients (0.8%) due to autoimmune thyroiditis, and 83 patients (4.9%) for unknown reasons. TSH values before the diagnosis of cancer were available in 357 patients (21.1%). Median TSH before diagnosis of cancer was higher in patients with history of hypothyroidism compared with patients without history of hypothyroidism (2.1 vs. 1.2 μIU/ml; $p = 0.008$; Mann-Whitney U test). TSH higher than the ULN before cancer diagnosis was statistically more frequently observed in patients with history of hypothyroidism (14.6% vs. 4.1%; $p = 0.011$; chi Square test). fT3 values before the diagnosis of cancer were available for 125 patients (7.4%) and fT4 values for 234 patients (13.8%). fT3 and fT4 values were not different between patients with and without history of hypothyroidism ($p > 0.05$; Mann-Whitney U test).

Female patients presented more frequently with a history of hypothyroidism (12.0% vs. 3.1%; $p < 0.001$; Chi Square test). In line, hypothyroidism was most frequently observed among patients with breast cancer (49/411; 11.9%) followed by lung cancer (78/1183; 6.5%) and patients with melanoma (6/98; 6.1% $p = 0.001$; chi Square test; Table 3). Presence of the endothelia growth factor receptor (EGFR) mutation had no impact on the frequency of hypothyroidism in the patients with non–small-cell lung cancer BMs. Three of 12 (25%) patients with history of hypothyroidism presented with EGFR mutation and 23 of 106 (21.7%) patients without history of hypothyroidism presented with EGFR mutation ($p > 0.05$; chi Square test).

3.2.2. Validation cohort

Eighteen patients (9.4%) were diagnosed with hypothyroidism and 2 patients (1.0%) with hyperthyroidism before the diagnosis of cancer (Table 2). Breast cancer patients presented more frequently with hypothyroidism (1/4; 25.0%) than lung cancer (14/172; 8.1%), or melanoma (2/14; 14.3%) patients ($p = 0.009$; chi Square test). Frequency of hypothyroidism did not differ by sex ($p = 0.182$; chi Square test; Table 4).

3.3. Correlation of thyroid function with clinical course in the discovery cohort

Time from diagnosis of primary tumour to BM diagnosis was longer in patients with a history of hypothyroidism (median 14 months, 95% confidence interval [CI]: 10–23) than in patients without a history of hypothyroidism (median 8 months, 95% CI: 7–9; $p = 0.014$; log rank test; Fig. 1A). No correlation with time to BMs development was evident for history of hyperthyroidism (8 vs. 14 months; $p = 0.908$; log rank test).

Extracranial disease burden did not differ between patients with (88/136; 64.7%) versus patients without (924/1571; 58.8%; $p = 0.180$; chi Square test) hypothyroidism. In line, median number of involved extracranial organs did not correlate with history of hypothyroidism ($p = 0.777$; Mann-Whitney U test). Further, no difference in the number of BMs at diagnosis ($p = 0.583$; chi square test) or in the DS-GPA class ($p = 0.849$; chi square test) in accordance with history of hypothyroidism was observed (Table 3).

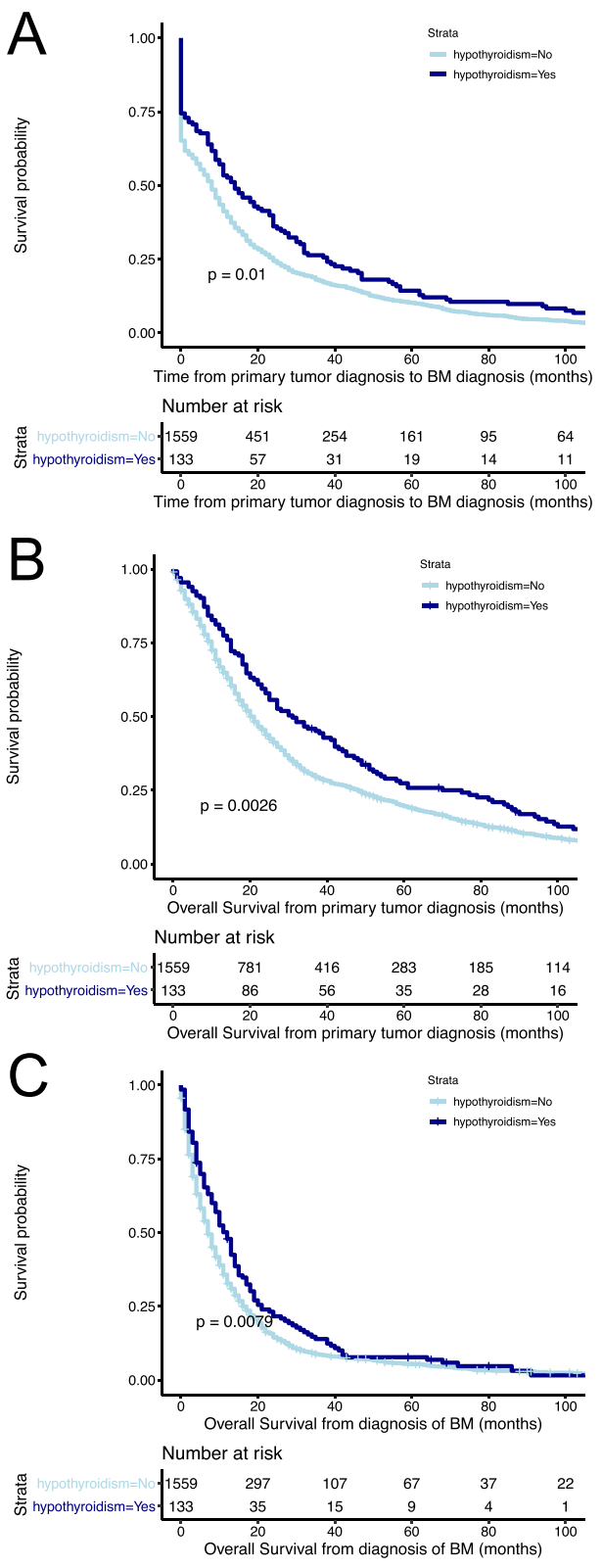

Fig. 1. Association of hypothyroidism and survival times in the discovery cohort: Time from diagnosis of cancer to diagnosis of BMs (A), as well as survival from diagnosis of cancer (B) and from diagnosis of BMs (C) was longer in hypothyroid patients.

TSH values at diagnosis of BM were available in 892 patients (52.7%), fT3 values in 149 patients (8.8%), and fT4 values in 585 patients (34.6%). Median TSH and median fT3 did not differ between patients with and without history of hypothyroidism. fT4 values at diagnosis of BM were higher in patients with a history of hypothyroidism (1.5 versus 1.2 ng/dl; $p < 0.001$; Mann-Whitney U test).

TSH values after radiotherapy were available in 936 patients (55.3%) patients. Twelve (1.3%) of these patients developed hypothyroidism after radiotherapy for BMs and needed TH replacement therapy. Six of 441 (1.4%) patients developed hypothyroidism after stereotactic radiosurgery, 6 of 179 (3.3%) after whole-brain radiotherapy, whereas none of the patients treated with neurosurgery without further radiation, chemotherapy or best supportive care developed hypothyroidism ($p > 0.05$; chi square test). None of the investigated patients presented with newly onset hyperthyroidism during cancer treatment.

3.4. Correlation of thyroid function with survival

3.4.1. Discovery cohort

History of hypothyroidism before diagnosis of cancer was associated with longer survival from diagnosis of cancer (median 31 months, 95% CI: (25–42) vs. median 21 months, 95% CI: (19–22); $p = 0.0026$; log rank test; Fig. 1B): and with longer survival from diagnosis of BMs (median 12 months, 95% CI: (9–14) vs. median 7 months, 95% CI: (7–8); $p = 0.0079$; log rank test; Fig. 1C). Cause of hypothyroidism and survival from diagnosis of cancer showed no association ($p = 0.310$; log rank test), although numerically patients with history of autoimmune thyroiditis had longer survival time (median: 54 months) than patients with unknown cause (median: 30 months) or thyroid surgery (median: 32 months).

As history of hypothyroidism correlated with sex and primary tumour type, multivariate analysis including history of hypothyroidism, sex, primary tumour type, as well as the established prognostic score DS-GPA was performed to analyse whether history of hypothyroidism is statistically independently associated with survival prognosis. In multivariate analysis including DS-GPA (hazard ratio [HR]: 1.48; 95% CI (1.38–1.58); $p < 0.0001$), primary tumour type (breast cancer) (HR: 1.20; 95% CI: (0.83–1.74); $p = 0.3342$), primary tumour type (melanoma) (HR: 2.85; 95% CI: (1.58–5.17); $p = 0.0005$), and sex (HR: 0.900; 95% CI: (0.801–1.010); $p = 0.074$), history of hypothyroidism before diagnosis of cancer was independently associated with survival after diagnosis of BM (HR: 0.76; 95% CI: (0.63–0.91); $p = 0.0034$; Cox regression model). The association of hypothyroidism with survival after diagnosis of BM was observed to be homogeneous across the subgroups formed by the predefined factors of

Table 4
Clinical differences in patients with and without history of hypothyroidism in the validation cohort.

Characteristics		Patients with history of hypothyroidism (n = 18)		Patients without history of hypothyroidism (n = 173)		P value
		N	%	N	%	
Age at diagnosis of BM, years	Median	55.5		64		0.040
	Range	33.76		31–89		
Sex	Male	8	44.4	105	60.7	0.182
	Female	10	55.6	68	39.3	
Cancer entity	Lung cancer	14	77.8	158	91.3	0.009
	Breast cancer	1	5.6	3	1.7	
	Melanoma	2	11.1	12	6.9	
	Parotid tumour	1	0.5	0	0	

interest, although less for patients in DS-GPA class I. Nevertheless, all confidence intervals in the subgroups of interest cover the regression coefficient (RC) estimate in the full population indicating consistent results across subgroups. In detail, history of hypothyroidism was associated with survival prognosis in the subgroups of male (RC: -0.28; 95% CI: −0.72 to 0.15), female (RC: -0.20; 95% CI: −0.40 to 0.01), patients with lung cancer (RC -0.27; 95% CI −0.51 to 0.04), patients with breast cancer (RC: -0.12; 95% CI: −0.42 to 0.19), patients with melanoma (RC: -0.74; 95% CI −1.65 to 0.18), as well as patients with DS-GPA class I (RC: 0.22; 95% CI: −0.29 to 0.73), class II (RC: -0.36; 95% CI: −0.68 to −0.03), class III (RC: -0.25; 95% CI: −0.55 to 0.05) and class IV (RC: -0.40; 95% CI: −0.82 to 0.02]; Fig. 2).

3.5. Validation cohort

In line with the discovery cohort, patients with hypothyroidism had longer overall survival from primary tumour diagnosis (median: 55 months, 95% CI: 40-NA) than patients without hypothyroidism (median: 11 months, 95% CI: 7–15; p = 0.00058; log rank test; Fig. 3A). Further, patients with hypothyroidism had longer overall survival from diagnosis of BM (median: 40 months, 95% CI: 36-NA) than patients without hypothyroidism (median: 10 months, 95% CI: 7–15; p = 0.0036; log rank test; Fig. 3B).

4. Discussion

The association of thyroid function and cancer progression has been addressed by several preclinical and

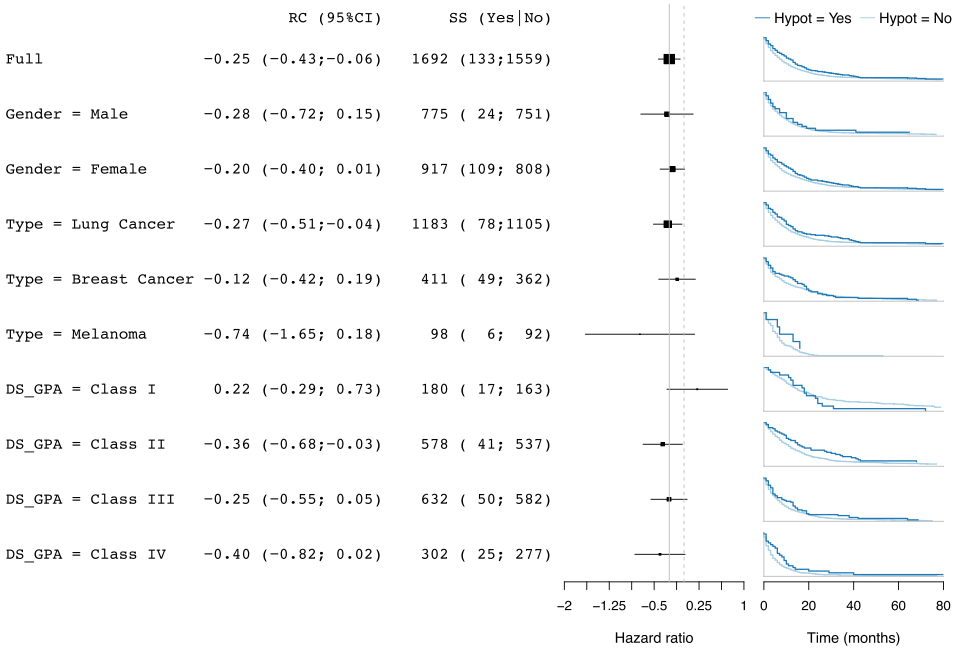

Fig. 2. Association of hypothyroidism across subgroups defined by multiple factors with survival time from diagnosis of brain metastases in the discovery cohort. RC = regression coefficient. Sample Size (SS) is given for each subgroup and further divided based on their history of hypothyroidism.

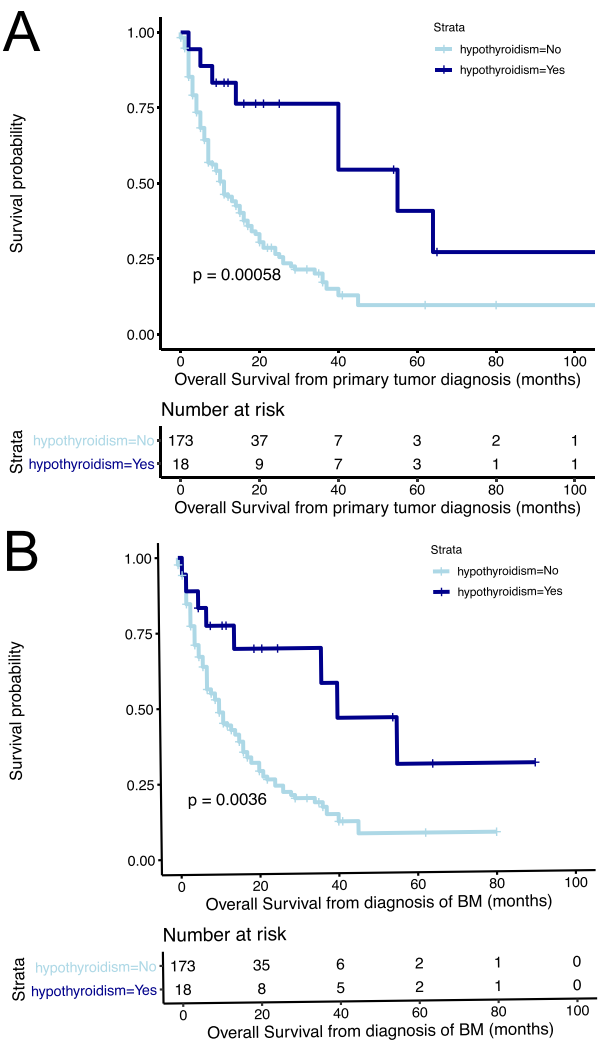

Fig. 3. Association of hypothyroidism and survival in the validation cohort: Overall survival from diagnosis of cancer (A) and from diagnosis of BMs (B).

epidemiological studies, however, the present study identifies a prognostic role of thyroid function in two independent cohorts of patients with brain metastatic cancer [5,7]. History of hypothyroidism was associated with slowed disease progression as hypothyroid patients presented with a longer survival from diagnosis of cancer, a longer time until development of BMs, as well as a longer survival from diagnosis of BMs in the discovery and independent validation cohort.

Previous epidemiological studies postulated that hypothyroid breast cancer patients are older at diagnosis, indicating that TH depletion might slow down cancer development and progression [8]. However, other epidemiological studies e.g. in patients with ovarian cancer reported conflicting results suggesting that hyperthyroidism and overall history of hypothyroidism are associated with worse 5-year survival [11]. A case report of a patient suffering from metastatic non–small-cell lung cancer surviving a myxoedema coma and subsequent stabilization of cancer progression for more than 5 years, was the basis for clinical attempts to interfere with TH signalling in patients with cancer [12]. Chemical hypothyroidism was induced successfully using the antithyroid thioamide, i.e. propylthiouracil, followed by carboplatin chemotherapy or tamoxifen therapy in patients with glioblastoma, however efficacy data are not yet sufficiently available to evaluate clinical activity [13,14]. The present investigation represents a large investigation of thyroid function in patients with metastatic cancer. Our data supports the clinical relevance of TH signalling in cancer; however causal relation cannot be proven by the present data as prospective clinical trials are needed to investigate an actual clinical impact rather than mere association. Certainly, the induced hypothyroid state has to be induced with caution and patients should not experience related symptoms. Indeed, the patients in the present cohort were all substituted resulting in a normalization of TSH values but slightly increased fT4 values. In consequence, strategies actively inducing light, subclinical hypothyroidism or restricted TH replacement in patients with hypothyroid cancer could be investigated.

We can only speculate on the mechanistical explanations of the association of hypothyroidism with survival in patients with cancer. Insights from preclinical animal models indicate that the tumour suppressing effect of hypothyroidism might be mediated via the αvβ3 integrin signalling pathway, as THs regulate the expression of a large panel of genes relevant to cancer cell proliferation, cancer cell survival and tumour-linked angiogenesis [15,16]. αvβ3 integrin expression can be more frequently observed on BMs tumour cells compared with the matched primary tumour, supporting the theory that activation might be associated with metastatic spread [17]. Indeed, preclinical inhibition of integrin signalling using an αv antibody resulted in smaller and less invasive BMs growth [18,19]. Further mechanistical research is needed to identify the causal relations and potential treatment targets in the TH signalling cascade in cancer.

Patients with a history of hypothyroidism more frequently had TSH values higher than the ULN. However, all patients received treatment and therefore the majority of TSH values, also in patients with history of hypothyroidism, presented within the NR. The standard thyroid substitution is a T4 formulation and as a pro-hormone, T4 must be converted to T3 in the tissue by iodothyronine deiodinases to acquire biological activity [20]. Patients treated with levothyroxine (T4) were shown to not achieve serum levels of T3 within the NR owing to inadequate conversion, which results in a high T4/T3 serum ratio [21]. In contrast to peripheral tissues, the hypothalamus is less susceptible to an increased T4/T3 ratio and in consequence the TSH is normalized before adequate T3 availability can be achieved in the peripheral tissues. Animal studies suggest that actually

the combination of levothyroxine (T4) plus liothyronine (T3) could normalize mitochondrial content and α-glycerophosphate dehydrogenase activity – both markers of T3-responsiveness in the liver and skeletal muscle – and circulating cholesterol concentrations better than levothyroxine (T4) treatment alone [22]. Therefore, the observed association of hypothyroidism with survival despite the levothyroxine substitution and a normalized TSH value, might be caused by and inadequate T4/T3 ratio, preserving a hypothyroid status in the tumour tissue. A more detailed examination of TSH, fT3 and fT4 values, as well as an assessment of the presence of autoimmune antibodies in a prospective cohort would be of interest to further identify the underlying cause of the association of survival and hypothyroidism; however due to the retrospective design not all parameters were available in the entire cohort. Although the validation cohort could support the investigated correlation of hypothyroidism and survival, the available clinical data were limited compared with the discovery cohort. Nevertheless, given the clear same prognostic association in this independent cohort, treated at a different center in a different country, strongly supports the observed association of thyroid function of survival prognosis in patients with BMs.

5. Conclusions

In conclusion, we report an association of thyroid function and survival in a well characterized, large cohort, as well as in an independent validation cohort of patients with metastatic cancer. Our data supports the theory that TH withdrawal might impede cancer growth via the interference with pro-neoplastic molecular pathways, although causal relation have to be addressed in subsequent preclinical studies [5]. Investigation of the underlying molecular mechanisms might allow the identification of promising new treatment targets. Further studies, specifically investigating the underlying pathways are needed to draw potential therapeutic conclusions and design trials investigating targeted therapies.

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Conflict of interest statement

A.S.B. has received research support from Daiichi Sankyo (≤10000€), Roche (>10000€); has received honoraria for lectures;has been a member of the consultation or advisory board participation from Roche Bristol-Meyers Squibb, Merck, Daiichi Sankyo (all < 5000€), has received travel support from Roche, Amgen and AbbVie. M.K. has received research support from Sanofi, AstraZeneca and Ipsen; served as a speaker and received consulting fees from AstraZeneca, Novartis, Novo Nordisk, Lilly, Merck, Böhringer, Roche and Sanofi. M.W. has received research grants from Abbvie, Adastra, Bristol Meyer Squibb (BMS), Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Piqur and Roche; has received honoraria for lectures or served as a member of advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb (BMS), Celgene, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen. M.P. has received research support from Böhringer-Ingelheim, GlaxoSmithKline, Merck Sharp & Dome and Roche; has received honoraria for lectures; served as a member of the consultation or advisory board participation (all < 5000€) from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Merck Sharp & Dome. All the other authors have no conflicts of interest to declare.

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